Cause-specific mortality associated with HIV and HTLV-II infections among injecting drug users in the USA

James J. Goedert, Michael W. Fung, Susanne Felton[a], Robert J. Battjes[b] and Eric A. Engels

Background: Human T-lymphotropic virus type II (HTLV-II) is widespread among injecting drug users (IDU) and may contribute to the risk of leukemia/lymphoma, neurodegenerative disease, and perhaps pneumonia, especially with HIV co-infection.

Methods: In 1987–1991, 6570 IDU were tested for HIV and HTLV-II antibodies. In 1998, they were matched to the National Death Index. Numbers of observed deaths of each cause were compared by standardized mortality ratios with the numbers expected, using sex-, race-, age-, and year-specific rates in the general population. Relative risk (RR) associated with each virus, compared to uninfected drug users, was estimated by Poisson modeling.

Results: There were 1351 deaths, including 683 (15%) of 4604 participants who enrolled seronegative for both viruses; 328 (47%) of 701 who had HIV but not HTLV-II infection; 220 (21%) of 1033 who had HTLV-II but not HIV infection; and 120 (52%) of 232 who were infected by both viruses. Compared to the general population, mortality for participants with neither virus was increased 4.3-fold [95% confidence interval (CI), 4.0–4.7] and was significantly elevated for virtually every cause of death. With HIV, mortality from medical causes, but not external causes, was increased 3.7-fold (95% CI, 3.3–4.2), particularly with AIDS and related conditions. With HTLV-II, all-cause mortality was reduced (RR, 0.8; 95% CI, 0.7–0.9), with no statistically significant reduction or elevation for any specific cause. A non-significant excess of tuberculosis deaths (RR, 4.6; 95% CI, 0.8–25.2) was noted with HTLV-II, but there was no excess mortality from leukemia/lymphoma, other malignancies, or neurodegenerative disease.

Conclusions: Without HIV or HTLV-II, IDU had profoundly increased mortality from medical and external causes. HIV was specifically associated with death due to AIDS and related conditions. HTLV-II infection was not significantly associated with mortality from any cause, suggesting that it is not a significant human pathogen, even when present with HIV infection.
© 2001 Lippincott Williams & Wilkins

AIDS 2001, **15**:1295–1302

Keywords: HIV infection, HTLV-II infection, injecting drug use, mortality, overdose, tuberculosis, pneumonia, cancer

From the Viral Epidemiology Branch, National Cancer Institute, Rockville, Maryland, [a]Research Triangle Institute, Washington DC, and [b]Friends Research Institute, Baltimore, Maryland (formerly with National Institute on Drug Abuse, Rockville Maryland), USA.

Requests for reprints to: J. J. Goedert, 6120 Executive Boulevard, Suite 8012, Rockville, Maryland 20852 USA.

Received: 14 December 2000; revised: 22 March 2001; accepted: 29 March 2001.

Introduction

Persons with HIV/AIDS are at high risk for serious complications of many types of infections, including infections that usually are innocuous for people with intact immunity. The spectrum of these complications continues to be defined. For example, Poiesz and colleagues recently described an HIV/AIDS patient who developed cutaneous T-cell lymphoma with clonal integration of human T-lymphotropic virus type II (HTLV-II) [1].

HTLV-II is a transforming human retrovirus that was first isolated from the transformed T cells of a patient with hairy-cell leukaemia [2]. Molecular sequencing of additional isolates revealed two strains – HTLV-IIa, which is highly prevalent among injecting drug users (IDU), and HTLV-IIb, which is endemic in certain Amerindian populations [3–11]. Like HIV and the prototype human retrovirus, HTLV-I, HTLV-II is transmitted through shared needles, transfusion of contaminated blood cells, sexual contact, and breast feeding [3]. HTLV-I infection is associated with adult T-cell leukemia and with HTLV-I-associated myelopathy (HAM). In contrast, HTLV-II appears to be fairly innocuous. It has been detected in a handful of patients with HAM, leukemias, or soft tissue infections, [11] but the rarity and heterogeneity of the conditions raise doubts about a link between HTLV-II and specific illnesses.

In the current study, we investigated how HTLV-II infection affected mortality, predominantly during the era before highly active antiretroviral therapy (HAART) was widely used, in a large population of IDU [4,5].

Methods

To evaluate risk factors and trends in HIV seroprevalence, the National Institute on Drug Abuse and the National Cancer Institute collected sera and questionnaire data from consenting clients admitted to selected methadone treatment programs in the following US cities: Baltimore, Chicago, Los Angeles, San Antonio, New York City, Asbury Park (New Jersey), Trenton (New Jersey), Philadelphia, and Miami. Participants were enrolled from March 1987 to December 1991 except those in Miami (discontinued in December 1988) and Philadelphia (started in March 1989). Participants from Miami were excluded from analysis because of early termination. Eligible participants were at least 18 years old and reported injection drug use within the preceding month.

As reported previously [4,5], the sera were screened for antibodies to HIV using a whole-virus enzyme immunoassay (EIA) (Du Pont NEN, Wilmington, Delaware, USA). HIV-reactive samples were confirmed by Western blot (Du Pont NEN). Sera were considered positive if antibodies were detected by Western blot to gp120/160 and to p24 or gp41. Sera were screened for HTLV-I and -II antibodies using a recombinant rp21e EIA (Cambridge Biotech, Worcester, Massachusetts, USA) and an HTLV -I whole-virus EIA (Du Pont NEN or Genetic Systems, Redmond, Washington. USA). Sera that were reactive in either EIA were tested by recombinant-enhanced HTLV-I Western blot (Biotech Research Laboratories, Rockville, Maryland, USA). Sera with Western blot reactivity against both p24 and rp21e were scored positive; the others were considered negative. HTLV-I and -II then were distinguished by synthetic peptide EIA (United Biomedical/Olympus, Hauppage, New York, USA), recombinant protein-enhanced Western blot (Diagnostic Biotechnology, Singapore), and, for a few samples, an algorithm comparing Western blot p24 and p19 band strength [5,12]. For the current analysis, each subject was categorized as seropositive for HIV, for HTLV-II, for both, or for neither. Reactivity against HTLV-I (2.4% of sera) was ignored.

We used the National Death Index Plus (NDI-Plus) program of National Center for Health Statistics to identify deaths in this cohort. NDI-Plus uses personal identifying information (name, social security number, birthday, etc.) to match to all deaths in the USA. Of the 7841 participants who enrolled and were tested for HTLV-I and -II, 6576 (83.9%) provided sufficient identifying information for submission to NDI-Plus. For the current analysis, NDI-Plus was complete through December 1998, providing 7–11.8 years of potential follow-up of the cohort.

Following the match, one duplicate record was found and deleted from the analysis. Three more were deleted because of conflicting sex information, and another two were deleted because their age at enrollment was greater than 69 years. The final analysis data set included 1351 decedents in a population of 6570 IDU aged 18–69 at enrollment. Race was categorized into white, black, and other.

For each matched subject, NDI-Plus provided the underlying cause of death, coded using the International Classification of Diseases, Ninth Edition, as abstracted from death certificates by trained nosologists. For analysis, the coded causes of death were collapsed into 11 medical [AIDS, malignancy, pneumonia, tuberculosis, septicemia, pulmonary (excluding pneumonia), circulatory, hepatic, alcohol/other drug abuse, miscellaneous, and ill-defined medical causes] and five external causes of death [accidental overdose, trauma (including motor vehicle accidents), homicide, suicide, and miscellaneous external causes]. The 16 categories did not overlap.

For each outcome, we compared the number of observed deaths with the number expected, where expected counts were calculated from sex-, race-, age-, and year-specific rates supplied by the National Center for Health Statistics for the eight counties where the participants enrolled. The standardized mortality ratio (SMR), calculated as observed counts divided by expected counts, served to measure risk in the cohort relative to the general population.

We also calculated these SMR separately for the four subgroups of the cohort defined jointly by HIV and HTLV-II status. This tabulation led us to estimate the effects of HIV and HTLV-II infections on mortality using the following regression model:

$$\log(\mathrm{SMR}_{i,j}) = \log(\mathrm{SMR}_{\mathrm{uninfected}}) + \beta_{\mathrm{HIV}} \times i + \beta_{\mathrm{HTLV}} \times j$$

where $\mathrm{SMR}_{i,j}$ is the SMR for the subgroup with HIV infection status equal to i (0 for uninfected, 1 for infected) and HTLV-II infection status equal to j (0 for uninfected, 1 for infected). Then $\mathrm{SMR}_{\mathrm{uninfected}}$ is the SMR for dually uninfected participants, and β_{HIV} and β_{HTLV} are the separate additional effects of HIV and HTLV-II infection, respectively. Under this model, the relative risks associated with HIV and HTLV-II infection are thus $\exp(\beta_{\mathrm{HIV}})$ and $\exp(\beta_{\mathrm{HTLV}})$, respectively. To fit this model, we assumed a Poisson likelihood for observed cases and derived maximum likelihood estimates and confidence intervals for $\mathrm{SMR}_{\mathrm{uninfected}}$, β_{HIV}, and β_{HTLV}.

Results

Among 6570 IDU in the cohort, 933 (14%) were HIV seropositive and 1265 (19%) were HTLV-II seropositive. As noted previously, [4,5] participants with HTLV-II were much more likely to be older and black. NDI-Plus matching identified 1351 (20.6%) deaths after a mean follow-up of 6.7 years. These included 683 (14.8%) of 4604 participants who enrolled seronegative for both viruses, 328 (46.8%) of 701 who were seropositive for HIV but not HTLV-II, 220 (21.3%) of 1033 who were seropositive for HTLV-II but not HIV, and 120 (51.7%) of 232 who were seropositive for both viruses (Table 1). Among HTLV-II seronegative participants, the crude mortality rate, unadjusted for age and race, was increased 3.6-fold with HIV (11.8/3.3 deaths per 100 person years, Table 1). Among HIV seronegative participants, it was increased 1.5-fold with HTLV-II (4.8/3.3 deaths per 100 person-years; Table 1).

The leading causes of death were AIDS (n = 330), accidental overdose (n = 186), circulatory conditions (n = 184), and malignancy (n = 113). Under our regression model, all-cause mortality was higher in uninfected participants than in the general population [SMR 4.3, 95% confidence interval (CI), 3.9–4.7]. Moreover, the SMR among uninfected participants was significantly elevated for virtually every cause of death (Table 2). In particular, the SMR among uninfected participants was elevated for AIDS (SMR, 1.8; 95% CI, 1.4–2.3, Table 2), but participants may have become infected during the 84–142 months of follow-up. Only death due to tuberculosis (zero events) was not increased in participants who enrolled uninfected (SMR, 0.97; 95% CI, 0.17–5.58). For these uninfected IDU participants, the highest SMR were for accidental overdose (25.2), alcohol/other drug abuse (13.3), hepatic disease (11.3), sepsis (9.3), and miscellaneous external (9.5) causes of death (Table 2).

Poisson modeling indicated that, compared to HIV/HTLV-II uninfected IDU, HIV seropositive IDU had a significantly elevated relative risk (RR) for medical causes of death (RR, 3.7; 95% CI, 3.3–4.2) but not for external causes of death (RR, 0.9; 95% CI, 0.6–1.2;

Table 1. Characteristics of the 6570 participants in the cohort according to HTLV-II and HIV status at enrollment.

	Virus infection status			
	HIV negative/HTLV-II negative (n = 4604)	HIV positive/HTLV-II negative (n = 701)	HIV negative/HTLV-II positive (n = 1033)	HIV positive/HTLV-II positive (n = 232)
Male [n (%)]	3025 (65.7)	479 (68.3)	685 (66.3)	145 (62.5)
Age [years; mean (SD)]	34.6 (7.0)	35.7 (5.9)	42.1 (8.9)	39.4 (7.1)
Race				
Black (%)	1583 (34.1)	414 (59.1)	596 (57.7)	197 (84.9)
White (%)	1685 (36.6)	117 (16.7)	125 (12.1)	13 (5.6)
Other (%)	1336 (29.0)	170 (24.3)	312 (30.2)	22 (9.5)
Duration of follow-up [mean years (SD)]	6.8 (1.5)	5.8 (2.3)	6.7 (1.7)	5.8 (2.5)
Deaths [n (%)]	683 (14.8)	328 (46.8)	220 (21.3)	120 (51.7)
Mortality rate (deaths per 100 person years)	3.3	11.8	4.8	14.3

Table 2. Standardized mortality ratio (SMR) and relative risk (RR) of death from various causes with HTLV-II and HIV infection at enrollment.[a]

Cause of death	Deaths (n)	SMR for uninfected	95% confidence interval	HTLV-II effect (RR)	95% confidence interval	HIV effect (RR)	95% confidence interval
All medical causes	1011	4.30	3.94–4.69	0.82	0.71–0.94	3.71	3.27–4.21
Alcohol, other drug abuse	68	13.33	9.82–18.10	1.51	0.92–2.49	0.66	0.31–1.37
Hepatic disease	103	11.33	9.01–14.26	0.73	0.45–1.16	0.91	0.52–1.61
Malignancy	113	3.23	2.52–4.13	0.94	0.64–1.38	1.32	0.80–2.16
AIDS	330	1.83	1.44–2.32	0.98	0.76–1.26	*18.52*	*14.21–24.13*
Tuberculosis	6	0.97	0.17–5.58	4.62	0.84–25.23	*8.51*	*1.56–46.53*
Sepsis	24	9.32	5.04–17.25	0.38	0.13–1.13	*5.97*	*2.68–13.34*
Pneumonia	30	3.74	2.15–6.51	1.41	0.68–2.93	*3.84*	*1.87–7.91*
Pulmonary disease	24	5.75	3.33–9.92	1.16	0.51–2.61	0.81	0.24–2.73
Circulatory disease	184	4.61	3.85–5.53	*0.63*	*0.46–0.87*	1.06	0.71–1.59
Ill-defined causes	28	6.33	3.88–10.34	1.07	0.45–2.51	*2.34*	*1.06–5.19*
Miscellaneous medical causes	101	4.59	3.55–5.94	0.65	0.41–1.03	*2.50*	*1.64–3.80*
All external causes	340	9.84	8.71–11.12	0.79	0.59–1.05	0.86	0.63–1.18
Accidental overdose	186	25.15	21.34–29.64	0.77	0.52–1.14	0.71	0.45–1.10
Suicide	23	5.95	3.88–9.12	0.00	–	0.76	0.18–3.25
Homicide	49	4.01	2.89–5.57	0.98	0.48–2.03	0.85	0.38–1.90
Other trauma	40	5.74	3.96–8.33	0.94	0.43–2.03	1.35	0.60–3.07
Miscellaneous external causes	42	9.54	6.66–13.67	0.77	0.36–1.66	1.05	0.47–2.38
Circulatory	184	4.61	3.85–5.53	0.63	0.46–0.87	1.06	0.71–1.59
Atherosclerosis	62	3.25	2.35–4.48	0.77	0.46–1.30	0.58	0.23–1.44
CNS Hemorrhage	42	5.74	3.85–8.57	0.69	0.35–1.34	*2.03*	*1.02–4.04*
Hypertension	19	2.64	1.40–4.98	1.18	0.48–2.94	1.35	0.45–4.07
Cardiomyopathy	18	6.80	4.16–11.09	0.29	0.07–1.27	0.00	–
Valvular disease	14	11.86	6.34–22.17	0.40	0.09–1.79	1.48	0.41–5.32
Other circulatory	29	6.99	4.50–10.85	0.49	0.20–1.21	1.14	0.44–3.00

[a]The one medical cause of death associated with HTLV-II and the seven medical causes associated with HIV are indicated by italic type. CNS, Central nervous system.

Table 2). Among the medical causes, HIV was associated with an increased RR for death due to AIDS (18.5), tuberculosis (8.5), sepsis (6.0), pneumonia (3.8), ill-defined causes (2.5) and miscellaneous causes (2.5). RR for other causes of death were not significantly elevated or reduced (RR range, 0.7–1.4).

Surprisingly, HTLV-II seropositive IDU had a significantly reduced RR for all causes of death combined (RR, 0.8; 95% CI, 0.7–0.9) and specifically for circulatory causes (RR, 0.6; 95% CI, 0.5–0.9, Table 2). RR were reduced for six other causes, but not significantly. These included accidental overdose (0.8), hepatic disease (0.7), miscellaneous (0.7), sepsis (0.4), and suicide (zero cases). The highest RR for the HTLV-II seropositive participants was for tuberculosis death (RR, 4.6; 95% CI, 0.8-25.2), based on three cases. Three causes of death had slightly but non-significantly elevated RR: alcohol/other drug abuse (RR, 1.5), pneumonia (RR, 1.4), and other pulmonary conditions (RR, 1.2) (Table 2).

We further categorized circulatory causes of death into six non-overlapping subgroups. The 184 deaths in the cohort included atherosclerosis (n = 62), central nervous system hemorrhage (n = 42), hypertension (n = 19), cardiomyopathy (n = 18), valvular disease (n = 14), and other circulatory causes (n = 29). Participants who were uninfected at enrollment had significantly increased SMR for all six circulatory subgroups (SMR range, 2.6–11.9). HIV infection at enrollment did not significantly affect mortality in these circulatory subgroups, except for an increased risk of central nervous system hemorrhage (RR, 2.0; 95% CI, 1.0–4.0). With HTLV-II at enrollment, all circulatory subgroup RR were reduced non-significantly (range, 0.3–0.8) except for hypertension (RR, 1.2; 95% CI, 0.5–3.0).

Black patients accounted for 42% of the population (Table 1). To eliminate possible uncontrolled confounding by race, the SMR and RR analyses were repeated, restricted to the subgroup of black participants, among whom there were 686 deaths. Although the CI were wider, the point estimates for the SMR and RR associated with HTLV-II and HIV were very similar to those in Table 2 (data not shown).

Because HTLV-II has been noted with T-cell leukemia and lymphoma and with neurodegenerative diseases such as HAM, the malignant and miscellaneous causes of death were considered in greater detail. Of the 1351 total deaths, two (0.15%) were attributed to 'motor neuron disease'. One of these decedents was negative for both HTLV-II and HIV; the other was HTLV-II seropositive, HIV-seronegative at enrollment. No other cause of death resembled a spinal, demyelinating, or neurodegenerative disease such as HAM. The 43 cancer deaths among HTLV-II seropositive participants included one multiple myeloma case and one lymphoma case, similar to the distribution observed in the participants who were seronegative for both viruses (Table 3). For 19 cancer deaths among HIV seropositive participants, eight were attributed to lung cancer, three to lymphoma, and none to Kaposi's sarcoma.

Table 3. Frequencies of cancer deaths [n (%)], by HTLV-II and HIV status at enrollment.

	Virus infection status		
Site or type of cancer	HTLV-II negative/ HIV-negative	HTLV-II-positive[a]	HIV-positive[a]
Lymphoma	4 (7.0)	1 (2.3)	3 (15.8)
Hodgkin's disease	1 (1.8)	0	0
Leukemia	4 (7.0)	0	0
Multiple myeloma	0	1 (2.3)	0
Lung	13 (12.8)	15 (34.9)	8 (42.1)
Head and neck, larynx	0	3 (7.0)	0
Esophagus	2 (3.5)	1 (2.3)	0
Stomach	0	2 (4.7)	0
Pancreas	3 (5.3)	3 (7.0)	0
Liver	5 (8.8)	4 (9.3)	1 (5.3)
Colon, rectum, anus	6 (10.5)	2 (4.7)	2 (10.5)
Brain	4 (7.0)	0	0
Prostate	0	1 (2.3)	1 (5.3)
Breast	4 (7.0)	4 (9.3)	2 (10.5)
Cervix	3 (5.3)	2 (4.7)	0
Other specified	5 (8.8)	1 (2.3)	0
Unspecified	3 (5.3)	2 (4.7)	2 (10.5)
Total[a]	57	43	19

[a]Six cancer decedents who were HTLV-II positive and HIV positive were counted in both groups. These included two lung, one colon, one breast, and one unspecified type of cancer.

Discussion

We found no evidence that HTLV-II increases the risk of death from any cause. Our study contributes substantially to the HTLV-II literature, because of its size, its power to assess all causes of death, and its consideration of the impact of HIV co-infection. To assure ourselves of the study's validity, we compared mortality in our IDU cohort to that in the general population. All-cause mortality in the HTLV-II/HIV uninfected cohort was increased more than 5-fold. Moreover, SMR in this uninfected cohort were highest for conditions clearly associated with IDU, including accidental overdose, alcohol/other drug abuse, hepatic disease, trauma, and sepsis.

We found that HIV significantly increased the risk of death. Because there was little use of HAART among American drug users until at least 1997 [13] it is likely that such therapy had little effect on our results. The increased risks of death that we found were large and almost exclusively limited to AIDS (19-fold), tuberculosis (8.5-fold), sepsis (6-fold), and pneumonia (3.8-fold).

Our comparison of HTLV-II/HIV uninfected drug users to the closely matched local population revealed that medical causes of death were increased 4.30-fold and that external causes of death were increased 9.84-fold. In our view, this is likely to be a good estimate of the excess mortality that relates to factors associated with drug use other than HTLV-II and HIV. The excess risk for accidental overdose deaths was very large, 25-fold compared to the general population. HIV had no effect on the risk for overdose or other external causes of death or for most medical causes of death, except those related to AIDS. This supports the validity of our study but is at odds with previously reported cohort studies in Bologna, Rome, Amsterdam, and Baltimore, in which HIV was associated with a 4- to 10-fold increase in all-cause mortality including overdose [14–17]. Because HIV infection cannot affect the likelihood of overdose directly, we suspect that the previously reported association with overdose death is an artifact of residual confounding, that is, uncontrolled differences between HIV positive and HIV negative drug users.

All-cause mortality with HTLV-II appeared to be reduced by about 20% compared to that seen in uninfected IDU. However, this reduction was non-specific, as it affected nearly all causes of death. It should be noted that the effect of HTLV-II infection on mortality was estimated in our regression model by comparing the SMR for HTLV-II infected participants with the SMR for HTLV-II uninfected participants. Although both of these SMR were greater than one, their ratio was less than one; this is equivalent to saying that excess risk among HTLV-II positive participants was less than excess risk among HTLV-II negative participants. One possible explanation for this finding is the 'frailty bias' inherent to a study of a prevalent cohort. For example, among teenagers who began injection drug use before 1970, those who were most careless or susceptible to diseases may not have survived for 20 years to get into our cohort, leaving a hardier or lower risk subset over age 40 who were enrolled. HTLV-II prevalence was higher among older subjects (Table 1), so they might have seemed to be at lower excess risk than their younger counterparts. Nonetheless, if HTLV-II infection contributed to deaths among the young, frail people who did not enroll, it also should have had some similar effect among the survivors who did enroll; but no contribution of HTLV-II to death was found. In any event, because this downward bias in the risk estimates is likely small, we believe that we would have detected increased mortality from HTLV-II in our analyses if this virus actually did cause fatal outcomes.

One study of outpatients at San Francisco General Hospital and two analyses of volunteer American blood donors have found that HTLV-II was associated with disease morbidity. Modahl *et al.* noted that histories of pneumonia, abscess, and lymphadenopathy were more frequent in HTLV-II seropositive compared to age- and sex-matched HTLV-II seronegative IDU outpatients [14]. HTLV-II was not associated with disease in non-IDU outpatients, suggesting that HTLV-II may be a surrogate for other risk factors among IDU [18]. Among American blood donors, Murphy *et al.* reported that histories of bronchitis and of bladder or kidney infections, both before enrollment and during follow-up, were more frequent with HTLV-II infection [19,20]. Other conditions in the donors that were significantly associated with HTLV-II included: lymphadenopathy on the enrollment physical exam; histories of tuberculosis before enrollment, pneumonia before enrollment, and oral herpes during follow-up; and, marginally significant, history of pneumonia during follow-up [19,20]. In contrast, the occurrence during follow-up of bacterial pneumonia, infective endocarditis, and abscess did not differ between HTLV-II seropositive and seronegative IDU in Baltimore who were matched for age, HIV status, and duration of follow-up [21].

In our study, HTLV-II was associated with nonsignificantly increased risks of deaths attributed to pneumonia (RR, 1.4; 95% CI, 0.7–2.9) and tuberculosis (RR, 4.6; 95% CI, 0.8–25.2). We could have missed a stronger effect on pneumonia morbidity [23]. It is equally plausible, however, that these are chance findings or that HTLV-II is merely a surrogate for a lower socioeconomic status or higher risk lifestyle leading to pneumonia and tuberculosis through close personal

contact rather than through a biologic effect of HTLV-II.

Case reports suggest that HTLV-II contributes to neurodegenerative morbidity and mortality [20,22,24–27] and also to T-cell leukemia/lymphoma [1,2,28–30]. Despite these reports, our study suggests that very few deaths can be attributed to these diseases or to other conditions. One lymphoma death and one motor neuron disease death were found among 1265 HTLV-II seropositive participants with or without HIV. HTLV-II also has been associated with relative lymphocytosis [31,32] and lymph node enlargement [19]. This virus has tropism for and may clonally expand CD8 lymphocytes [1,30,33]. HTLV-II infected patients may have an expanded population of large granular lymphocytes that are not infected, perhaps due to indirect effects of the virus or to the effects of unrecognized conditions [30]. It is possible that a small fraction of such patients develop clinically evident leukemia or lymphoma, as observed among cows infected with bovine leukemia virus (BLV), the animal retrovirus most closely related to HTLV-I and -II. About one-third of BLV infected cows develop persistent lymphocytosis, whereas less than 5% develop clonal B-cell lymphoma [34]. No neurologic, pulmonary, or other diseases have been associated with BLV in cows.

In summary, we sought to identify causes of death that might be associated with HTLV-II infection by evaluating mortality among 1265 HTLV-II seropositive and 5305 HTLV-II seronegative IDU who were followed for up to 11.8 years. Participants who did not have HIV or HTLV-II at enrollment had substantially increased mortality due to alcohol/other drug abuse, hepatic disease, sepsis, miscellaneous external causes, and especially accidental overdose. These findings help to focus attention on and to set priorities for prevention of specific lethal conditions among all IDU, irrespective of HIV or HTLV-II infection. For HTLV-II seropositive participants, we found no evidence of increased mortality due to cancer or neurologic disease, which reinforces the conclusion that HTLV-II is not a significant human pathogen.

Acknowledgements

The authors thank M. Dotrang (Computer Science Corporation) and T. Helde and K. Lee (Information Management Services) for computer programming and especially the participating treatment programs and clients who made this study possible.

Sponsorship: The original field work was supported by National Institute on Drug Abuse contract 271-90-4000 with SRA Technologies. Current work was supported in part by National Cancer Institute contracts N02-CP-91027 and N02-CP-01004 with Research Triangle Institute. M. W. Fung's work was performed under the US Public Health Service Junior Commissioned Officer Student Training and Externship Program.

References

1. Poiesz B, Dube D, Dube S, *et al.* **HTLV-II-associated cutaneous T-cell lymphoma in a patient with HIV-1 infection.** *New England Journal of Medicine* 2000, **342**:930–936.
2. Kalyanaraman VS, Sarngadharan MG, Robert-Guroff M, *et al.* **A new subtype of human T-cell leukemia virus (HTLV-II) associated with a T-cell variant of hairy cell leukemia.** *Science* 1982, **218**:571–573.
3. Hall WW, Ishak R, Zhu SW, *et al.* **Human T lymphotropic virus type II (HTLV-II): epidemiology, molecular properties, and clinical features of infection.** *J Acquir Immune Defic Syndr Hum Retrovirol* 1996, **13** (suppl 1):S204–S214.
4. Cantor KP, Weiss SH, Goedert JJ, Battjes RJ. **HTLV-I/II seroprevalence and HIV/HTLV coinfection among U.S. intravenous drug users.** *J Acquir Immune Defic Syndr* 1991, **4**:460–467.
5. Briggs NC, Battjes RJ, Cantor KP, *et al.* **Seroprevalence of human T cell lymphotropic virus type II infection, with or without human immunodeficiency virus type 1 coinfection, among US intravenous drug users.** *J Infect Dis* 1995, **172**:51–58.
6. Black FL, Biggar RJ, Neel JV, Maloney EM, Waters DJ. **Endemic transmission of HTLV type II among Kayapo Indians of Brazil.** *AIDS Res Hum Retroviruses* 1994, **10**:1165–1171.
7. Switzer WM, Black FL, Pieniazek D, Biggar RJ, Lal RB, Heneine W. **Endemicity and phylogeny of the human T cell lymphotropic virus type II subtype A from the Kayapo Indians of Brazil: evidence for limited regional dissemination.** *AIDS Res Hum Retroviruses* 1996 **12**:635–640.
8. Biggar RJ, Taylor ME, Neel JV, *et al.* **Genetic variants of human T-lymphotropic virus type II in American Indian groups.** *Virology* 1996, **216**:165–173.
9. Ishak R, Harrington WJ, Jr, Azevedo VN, *et al.* **Identification of human T cell lymphotropic virus type IIa infection in the Kayapo, an indigenous population of Brazil.** *AIDS Res Hum Retroviruses* 1995, **11**:813–821.
10. Eiraku N, Novoa P, da Costa Ferreira M, *et al.* **Identification and characterization of a new and distinct molecular subtype of human T-cell lymphotropic virus type 2.** *J Virol* 1996, **70**: 1481–1492.
11. Murphy EL. **The clinical epidemiology of human T-lymphotropic virus type II (HTLV-II).** *J Acquir Immune Defic Syndr Hum Retrovirol* 1996, **13** (suppl 1):S215–S219.
12. Wiktor SZ, Alexander SS, Shaw GM, *et al.* **Distinguishing between HTLV-I and HTLV-II by western blot [letter].** *Lancet* 1990, **335**:1533–1533.
13. Anderson R, Bozzette S, Shapiro M, *et al.* **Access of vulnerable groups to antiretroviral therapy among persons in care for HIV disease in the United States.** HCSUS Consortium. HIV Cost and Services Utilization Study. *Health Serv Res* 2000, **35**:389–416.
14. Goedert JJ, Pizza G, Gritte FM, *et al.* **Mortality among drug users in the AIDS era.** *Int J Epidemiol* 1995, **24**:1204–1210.
15. Zaccarelli M, Pattari P, Rezza G, *et al.* **Impact of HIV infection on non-AIDS mortality among Italian injecting drug users.** *AIDS* 1994, **8**:345–350.
16. Van Haastrecht HJA, van Ameijden EJC, van den Haek JAR, Mientjes GHC, Bax JS, Coutinho RA. **Predictors of mortality in the Amsterdam cohort of human immunodeficiency virus (HIV)-positive and HIV-negative drug users.** *Am J Epidemiol* 1996, **143**:380–391.
17. Vlahov D, Tang AM, Lyles C, *et al.* **Increased frequency of overdose deaths among HIV-infected injection drug users.** *Addiction Res* 2000, **8**:311–326.
18. Modahl LE, Young KC, Varney KF, Khayam-Bashi H, Murphy EL. **Are HTLV-II seropositive injection drug users at increased risk of**

bacterial pneumonia, abscess, and lymphadenopathy? *J Acquir Immune Defic Syndr Hum Retrovirol* 1997, **16**:169–175.
19. Murphy EL, Glynn SA, Fridey J, *et al.* **Increased prevalence of infectious diseases and other adverse outcomes in human T lymphotropic virus types I- and II-infected blood donors.** *J Infect Dis* 1997, **176**:1468–1475.
20. Murphy EL, Glynn SA, Fridey J, *et al.* **Increased incidence of infectious diseases during prospective follow-up of human T-lymphotropic virus type II- and I-infected blood donors.** *Arch Intern Med* 1999, **159**:1485–1491.
21. Safaeian M, Wilson LE, Taylor E, Thomas DL, Vlahov D. **HTLV-II and bacterial infections among injection drug users.** *J Acquir Immune Defic Syndr Hum Retrovirol* 2000, **24**:483–487.
22. Mientjes GH, van Ameijden EJ, van den Hoek AJ, Coutinho RA. **Increasing morbidity without rise in non-AIDS mortality among HIV-infected intravenous drug users in Amsterdam.** *AIDS* 1992, **6**:207–212.
23. Murphy EL, Fridey J, Smith JW, *et al.* **HTLV-associated myelopathy in a cohort of HTLV-I and HTLV-II-infected blood donors.** *Neurology* 1997, **48**:315–320.
24. Hjelle B, Appenzeller O, Mills R, *et al.* **Chronic neurodegenerative disease associated with HTLV-II infection.** *Lancet* 1992, **339**:645–646.
25. Jacobson S, Lehky T, Nishimura M, Robinson S, McFarlin D, Dhib-Jalbut S. **Isolation of HTLV-II from a patient with chronic, progressive neurological disease clinically indistinguishable from HTLV-I-associated myelopathy/tropical spastic paraparesis.** *Am Neur Assoc* 1993, **14**:392–396.
26. Sheremata WA, Harrington WJ, Jr, Bradshaw PA, *et al.* Association of '(tropical) ataxic neuropathy' with HTLV-II. *Virus Res* 1993, **29**:71–77.
27. Black FL, Biggar RJ, Lal RB, Gabbai AA, Filho JP. **Twenty-five years of HTLV type II follow-up with a possible case of tropical spastic paraparesis in the Kayapo, a Brazilian Indian tribe.** *AIDS Res Hum Retroviruses* 1996, **12**:1623–1627.
28. Rosenblatt JD, Golde DW, Wachsman W, *et al.* **A second isolate of HTLV-II associated with atypical hairy cell leukemia.** *New Engl J Med* 1986, **315**:372–377.
29. Rosenblatt JD, Giorgi JV, Golde DW, *et al.* **Integrated human T-cell leukemia virus II genome in CD8+ T cells from a patient with "atypical" hairy cell leukemia: evidence for distinct T and B cell lymphoproliferative disorders.** *Blood* 1988, **71**:363–369.
30. Martin MP, Biggar RJ, Hamlin-Green G, Staal S, Mann D. **Large granular lymphocytosis in a patient infected with HTLV-II.** *AIDS Res Hum Retroviruses* 1993, **9**:715–719.
31. Schechter M, Harrison LH, Halsey NA, *et al.* **Coinfection with human T-cell lymphotropic virus type I and HIV in Brazil. Impact on markers of HIV disease progression.** *J Am Med Assoc* 1994, **271**:353–357.
32. Rosenblatt JD, Plaeger-Marshall S, Giorgi JV, *et al.* **A clinical, hematologic, and immunologic analysis of 21 HTLV-II infected intravenous drug users.** *Blood* 1990, **76**:409–417.
33. Ijichi S, Ramundo MB, Takahashi H, Hall WW**. In vivo cellular tropism of human T-cell leukemia virus type II (HTLV II).** *J Exp Med* 1992, **176**:293–296.
34. Rosenberg N, Jolicoeur P. **Retroviral pathogenesis.** In *Retroviruses.* Edited by Coffin JM, Hughes SH, Varmus HE. New York: Cold Spring Harbor Laboratory Press; 1997:475–585.